AR201-14045A

HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

2,2-bis(bromomethyl)-1,3-propanediol

CAS No. 3296-90-0

Submitted to the US EPA

By

Ameribrom, Inc.

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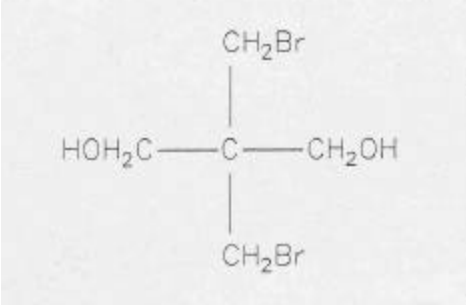
Test Plan for 2,2-bis(bromomethyl)-1,3-propanediol

1. General Information

1.1 CAS Number: 3296-90-0

1.2 Molecular Weight: 261.9

1.3 Structure and formula: $C_5H_{10}Br_2O_2$



1.4 Commercial Applications

2,2-bis(bromomethyl)-1,3-propanediol is used as a fire retardant in unsaturated polyester resins, in moulded products and in rigid polyurethane foam.

1.5 Worker/consumer exposure

Workers involved in both the manufacture of 2,2-bis(bromomethyl)-1,3-propanediol and of product containing the chemical are likely to have minimal exposure to the chemical as it is expected that good industrial hygiene practices will be followed and personal protective equipment worn to minimise exposure.

There are no direct consumer applications and therefore no direct sales to the general public. The most likely source of consumer exposure to 2,2-bis(bromomethyl)-1,3-propanediol is through fugitive dust from products containing the chemical.

2. Review of Existing Data and Development of Test Plan

Ameribrom, Inc. has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for 2,2-bis(bromomethyl)-1,3-propanediol.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available Adequate Data and Proposed Testing on 2,2-bis(bromomethyl)-1,3-propanediol

CAS No. 3296-90-0	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	?		Y		Y	N
Boiling Point	N						Y
Vapour Pressure	Y	N			Y	Y	N
Water solubility	N						Y
Partition Coefficient (Kow)	Y	?		Y		Y	N
Environmental Fate & Pathway							
Biodegradation	Y	?		Y		Y	N
Hydrolysis	N						Y
Photodegradation	N						Y
Transport and Distribution between Environmental Compartments	N						Y
Ecotoxicology							
Acute Fish	N						Y
Acute Daphnia	N						Y
Acute Algae	N						Y
Toxicology							
Acute Oral	Y	Y	Y			Y	N
Repeat Dose toxicity	Y	Y		Y		Y	N
Genetic toxicity – Gene mutation	Y	Y	Y			Y	N
Genetic toxicity – Chromosome aberration	Y			Y		Y	N
Reproductive toxicity	Y			Y		Y	N
Developmental toxicity/teratogenicity	N						Y

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The melting point of 2,2-bis(bromomethyl)-1,3-propanediol has been reported as 111-113°C in a peer reviewed publication.

2. Boiling Point

The boiling point of 2,2-bis(bromomethyl)-1,3-propanediol will be determined using OECD Method 103.

3. Vapour Pressure

Estimated as 1.3×10^{-5} mm Hg (1.7×10^{-3} Pa) using MPBPWIN v1.31 (EPIWIN modelling program).

4. Water solubility

The water solubility of 2,2-bis(bromomethyl)-1,3-propanediol will be determined using OECD Method 105.

5. Partition Coefficient

The partition coefficient (i.e. Kow) for 2,2-bis(bromomethyl)-1,3-propanediol has been reported as log Pow = 2.29 in a peer reviewed publication.

Summary of Physicochemical Properties Testing: The boiling point (OECD 103) and water solubility (OECD 105) of 2,2-bis(bromomethyl)-1,3-propanediol will be determined. Existing data for melting point, vapour pressure and partition coefficient are considered to fill these endpoints adequately.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

2,2-bis(bromomethyl)-1,3-propanediol has been shown to be not readily biodegradable (3-33% by BOD after 28 days) in a peer-reviewed study conducted using a Japanese MITI test.

2. Hydrolysis

The stability in water of 2,2-bis(bromomethyl)-1,3-propanediol will be determined using OECD Method 111.

3. Photodegradation

The potential for photodegradation of 2,2-bis(bromomethyl)-1,3-propanediol will be estimated using the Mackay Level III Fugacity Model.

4. Transport and Distribution between Environmental Compartments

The transport and distribution between environmental compartments of 2,2-bis(bromomethyl)-1,3-propanediol will be estimated using the Mackay Level III Fugacity Model.

Summary of Environmental Fate Testing: The stability in water (OECD 111) of 2,2-bis(bromomethyl)-1,3-propanediol will be determined. Photodegradation and transport and distribution between environmental compartments will be estimated using the Mackay Level III Fugacity Model. The existing data for biodegradability is considered to fill this endpoint adequately.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

The acute toxicity of 2,2-bis(bromomethyl)-1,3-propanediol to fish will be determined using OECD Method 203.

2. Acute Toxicity to Algae

The acute toxicity of 2,2-bis(bromomethyl)-1,3-propanediol to algae will be determined using OECD Method 201.

3. Acute Toxicity to Daphnia

The acute toxicity of 2,2-bis(bromomethyl)-1,3-propanediol to daphnia will be determined using OECD Method 202, part 1.

Summary of Ecotoxicity Testing: The acute toxicity to fish (OECD 203), algae (OECD 201) and daphnia (OECD 202, part 1) will be determined.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

The acute oral toxicity has been determined in two studies. The first study (OECD 401, rat, GLP) reported an LD50 value of > 2000 mg/kg b.w. The second study (method unclear, rat, no GLP), conducted using technical grade material, reported an LD50 value of 1880 mg/kg b.w.

2. Skin Irritation

This non-SIDS endpoint has been evaluated using a commercial grade of 2,2-bis(bromomethyl)-1,3-propanediol in a rabbit skin irritation test (U.S. Federal Register, §191.11, 1964). The substance was classified as mildly irritating to skin.

3. Eye Irritation

This non-SIDS endpoint has been evaluated using a commercial grade of 2,2-bis(bromomethyl)-1,3-propanediol in a test using New Zealand White rabbits (U.S. Federal Register, §191.12, 1964). The substance was classified as an eye irritant.

4. Repeat Dose Toxicity

Two repeat dose studies have been conducted under the National Toxicology Program using F344/N rats and B6C3F_1 mice. In a 13-week study, NOEL values of 1250 ppm (rats) and 625 ppm (male mice) were obtained. A NOEL value for female mice was not achieved. Dose-related effects seen were reduced body weight (rats/mice) and hypoactivity and abnormal posture (mice). Chemical-related lesions were observed only in the urinary bladder and kidney of rats and mice. Kidney lesions in mice (papillary necrosis and renal tubule regeneration fibrosis) were more severe than those observed in rats (papillary degeneration). Urinary bladder lesions in the mice were also more severe than in rats. In a 2-year study, NOAEL values were not achieved. LOAEL values of 2500 ppm (rats) and 312 ppm (mice) were obtained. Dose related effects included reduced body weight in rats, skin and subcutaneous tissue masses on the face, tail and the ventral and dorsal surfaces of rats and swelling, discharge and tissue masses involving the eye in mice. Survival of rats and mice was significantly reduced. This reduction was attributed primarily to the carcinogenic effects of the chemical. Numerous neoplasms were present in both rats and m ice. Based on these studies, it was concluded that there was clear evidence of carcinogenic activity in male and female F344/N rats and B6C3F_1 mice.

5. Genotoxicity

Three grades of 2,2-bis(bromomethyl)-1,3-propanediol (Commercial, 98.63% and 99.5%) have been tested for potential genotoxicity in the Ames Salmonella assay (OECD 471, strains TA1535, TA1537, TA98 and TA100, GLP). In each case, there was no evidence of mutagenic activity in the presence or absence of metabolic activation with rat S-9 mix, however there was clear evidence of mutagenic activity in strains TA1535 and TA100 in the presence of metabolic activation with hamster S-9 mix. A further, unreliable, study using lower concentrations of test substance also gave negative results in the presence and absence of metabolic activation using rat S-9 mix. 2,2-bis(bromomethyl)-1,3-propanediol did not induce sister chromatid exchanges when tested using

Chinese hamster ovary cells, either with or without metabolic activation using rat S-9 mix. However, it did induce chromosomal aberrations in Chinese hamster ovary cells in the presence of rat S-9 mix. The results of an in vivo mouse bone marrow micronucleus study using male mice was equivocal, but in a second study 2,2-bis(bromomethyl)-1,3-propanediol was found to induce micronuclei in the bone marrow of female mice. In a mouse peripheral blood micronucleus test, performed using animals from the 13-week repeat dose study, 2,2-bis(bromomethyl)-1,3-propanediol caused significant increases in micronucleated normochromatic erythrocytes in males and females.

6. Reproductive and Developmental Toxicity

The reproductive toxicity of 2,2-bis(bromomethyl)-1,3-propanediol in CD-1 mice has been evaluated in a 2-generation, GLP study using the NTP Fertility Assessment by Continuous Breeding system. In both the F_0 and F_1 studies, NOEL (adult) = 0.1%, NOEL (offspring) = 0.1%. When administered at the highest dose level (0.4%), reproduction was adversely affected. A cross over mating study showed that it was the reproductive performance of females that was adversely affected. Continued treatment resulted in a significant drop in body weight. The reproductive performance of second generation mice was adversely affected, with respect to the number of live pups per litter and the adjusted live pup weight.

The developmental toxicity of 2,2-bis(bromomethyl)-1,3-propanediol in rabbits will be determined using OECD Method 414.

Summary of Human Health Effects Testing: All human health effects endpoints have been filled adequately apart from developmental toxicity. This endpoint will be determined using OECD 414.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch et al (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

1. MPBPWIN v1.31. EPIWIN Modelling Program. Meylan, W. & Howard, P. (1999), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

2. USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

3. Klimisch, H-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

4. USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.